

REMARKS

Claims 1-3, 10-18 and 20 are withdrawn from consideration. Claims 4, 6-8 and 19 were previously under consideration. New claim 21 is added in this amendment.

Claims 4 and 19 have been amended more clearly define the invention. Claim 6 has been amended to correct its dependency.

New claim 20 is supported by specification, for example at pages 16 and 24-31.

No new matter has been added.

Applicants appreciate the Examiner's summary of various matters such as the status the application's priority claim, the declaration, the IDS, the prior claim objections and the drawings.

Applicants appreciate that Examiner's withdrawal of the rejections under 35 U.S.C. §102(a) and §102(a).

Rejections Under 35 U.S.C. §112, first paragraph (enablement)

The Examiner rejected claims 4 and 6-8 as not enabled. The Examiner stated that the enablement is limited to:

A method for producing an antibody against an antigen, wherein the method comprises the steps of: (a) preparing a baculovirus that comprises a DNA which encodes an antigen or an epitope thereof; (b) infecting a host cell with the baculovirus of (a) to obtain a budding virus that expresses said antigen or an epitope thereof; (c) producing a transgenic mouse that comprises a gene encoding the baculovirus membrane protein gp64; (d) immunizing the transgenic mouse of (c) with a fraction comprising the budding virus of (b); and (e) recovering an antibody specific for said antigen" from the immunized transgenic mouse.

The Examiner argued that broader claims where the transgenic mouse comprises a gene encoding any background antigen are not enabled. The basis for the Examiner's position is that "the art of producing a transgenic mouse with a specific phenotype is highly unpredictable in the art."

As explained previously, the methods of the present invention do not rely on the ability of the transgenic mice to exhibit a complex phenotype. Instead, the transgenic mice need only express the transgene at the rather low level required to induce immunotolerance.

The Examiner previously cited a variety of references suggesting that it can be challenging to produce certain phenotypes. However, even granting that this is the case, the Examiner has failed to articulate why these challenges apply to the present claims.

As explained in greater detail below, most of the references cited by the Examiner are relevant to the present claims.

Sigmund, for example, discusses the impact of genetic background on phenotypes such as ethanol tolerance, locomotor activity, atherosclerosis and renal development. Sigmund states that the site of gene insertion and genetic background can influence transgene expression and phenotype. However, Sigmund does not appear to suggest that it is difficult to simply obtain expression of the transgene.

Murray is concerned with the production of transgenic animals other than mice, e.g., transgenic livestock. Thus, the concerns raised by Murray are irrelevant to the present claims, which are limited to transgenic mice.

Larmere et al. state that 129 and C57BL/6 mouse strains can “display significant and sometimes extreme phenotypic differences.” However, Larmere et al.’s comments were in the context of transgenic mice used to study pain and analgesia. The phenotypes discussed by Larmere et al. relate to nociception, hypersensitivity and analgesia, all of which are complex phenotypes completely unrelated to the transgenic mice of the present claims. In any event, Larmere et al. state that the problem of differences between 129 and C57BL/6 stains can be minimized by using inbred strains.

Leiter discussed transgenic mice as models of Type I diabetes or Type II diabetes. This is a far more complex phenotype than the expression required to induce immunotolerance. Moreover, Leiter, like Larmere et al.,, discusses approaches for reducing the impact of genetic background on phenotype.

Houdebine et al. states that leaky expression of a transgene in mice can arise where the transgene is inserted into a region of the genome that causes the transgene to be expressed in tissues in which the promoter directly linked to the transgene is not expected to function. However, this concern is not relevant to the present methods, which do not depend on tightly regulated tissue-specific expression. Indeed, it is possible that widely distributed expression is an advantage when one wished to induce immunotolerance.

Kolb et al. is actually a far more relevant reference than the others because it concerns obtaining reliable expression of a transgene in mice rather than obtaining a particular phenotype. Kolb et al. states that conventional methods for introducing a transgene can lead to variable expression of the transgene due to positional effects related to chromatin structure. Kolb describes a biphasic strategy for introducing transgenes. According to Kolb et al., "the biphasic recombination strategy will automatically equip the inserted with the appropriate chromatin structure and regulatory elements require for its abundant expression and overcomes many of the difficulties associated with randomly integrated transgenes." This publication, which represents knowledge of those in the art, suggests that techniques are available to obtain abundant expression of transgenes. Kolb et al. certainly does not suggest that their technique eliminates difficulties with generating specific phenotypes, only that it provides a widely applicable way to obtain high level expression of a transgene in mice. Thus, Kolb et al. actually supports Applicants' position that it is not particularly difficult to obtain transgene expression in mice and contradicts the Examiner's position.

It is Applicants' position that the claims as amended are enabled. The presently claimed mice contain a transgene encoding a background antigen. Thus, rather than expressing the transgene so as to create a particular complex phenotype, the transgenic mice need only express as much of the antigen as required to induce immunotolerance. In fact, a similar result can commonly be achieved by administering a desired antigen to the mouse at the fetal stage or shortly after birth. Moreover, it is a simple matter to screen transgenic mice to identify those expressing the background antigen and having immunotolerance to the background antigen. Those skilled in the art are capable of carrying out such screening without undue experimentation.

Applicants note that even before the priority date of the present application, the art was aware of many examples of mice expressing a transgene. Such mice are described, for example, in *The University of Chicago Reporter*, Volume 2, Number 4 (2001) (provided under separate cover).

In view of the foregoing, Applicants request that these rejections under 35 U.S.C. §112, first paragraph be withdrawn.

Rejections Under 35 U.S.C. §112, second paragraph

The Examiner rejected claims 4 and 6-8 under 35 U.S.C. §112, second paragraph as indefinite. The Examiner stated that claim 4 did not provide proper antecedent basis for the recitation of “transgenic mouse” in steps (c) and (d). Applicants have amended claim 4 to provide proper antecedent basis.

Rejections Under 35 U.S.C. §112, first paragraph (new matter)

The Examiner stated that claims 4 and 19 include new matter because the specification does not provide literal support for the phrase “in an expressible manner”. The Examiner also argues that the claims are not enabled because “the claims only disclose ‘a gene encoding’ a particular polypeptide” in an expressible manner”

First, it is not necessary for the specification to provide *ipsis verbis* support for limitations of the claims. *Fujikawa v. Wattanasin* 93 F.3d 1559 (Fed. Cir. 1996). Thus, it is improper for the Examiner to reject the claims simply because the specification lacks literal support for the phrase “in an expressible manner.” However, to further prosecution, Applicants have amended the claims to delete the phrase “in an expressible manner.” Instead, claim 4 now specifies that “the mouse expresses the background antigen” and claim 19 now specifies that “the mouse expresses the baculovirus membrane protein gp64”.

Second, it is not necessary for the claims to actually recite the presence of expression control elements such as a promoter. The claims specify that the “mouse expresses the background antigen” (claim 4) or that “the mouse expresses the baculovirus membrane protein gp64” (claim 19). Those skilled in the art know how to make such mice and that certain elements for driving expression must be present. These details need not be recited in the claims.

It is believed that the claims are in condition for allowance.

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Respectfully submitted,

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